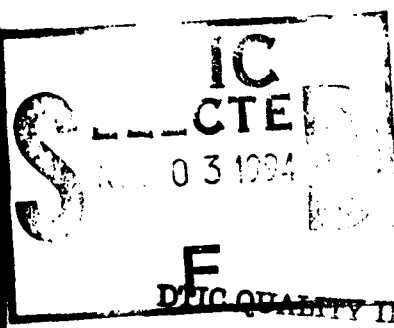




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Cerebral Salt-Wasting Associated With the Guillain-Barré Syndrome

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INAPPROPRIATE secretion of antidiuretic hormone has been implicated as the cause of the hyponatremia and renal salt-wasting associated with certain cases of intracranial and intrathoracic disease. Cases of traumatic, infectious, and neoplastic intracranial disease, and of neoplastic thoracic disease have been associated with the salt-wasting syndrome.¹⁻⁶ The following is a report of the simultaneous occurrence in a patient of an illness clinically indistinguishable from the Guillain-Barré syndrome and of an electrolyte disturbance marked by transient loss of renal sodium-conserving ability, plasma hypo-osmolality, and plasma hyponatremia. Immunologic features of this patient's illness suggested to us that the etiology of the polyradiculoneuropathy was hypersensitivity to viral antigens.

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Report of a Case

A 32-year-old Taiwanese man, a virology technician at the US Naval Medical Research Unit No. 2 (NAMRU-2), was admitted to Taiwan University Hospital on Sept 16, 1961, with the chief complaint of walking disturbance and pain in the left leg. About four days prior to admission he began to have headache, pain and numbness in the left thigh, and low backache. These symptoms progressed, the left leg became weak, and he had difficulty walking by the time of admission. The patient had no symptoms of upper-respiratory-tract infection or history of other antecedent illness. Rapidly ascending paralysis occurred during the next few days, and seven days after admission, he had complete quadriplegia and required respirator treatment. He was transferred to NAMRU-2 on Sept 23.

The patient had worked with group-B arboviruses from October 1960 to September 1961, the time of onset of illness. This work entailed pipetting virus suspensions, injecting animals, grinding up infected animal brains, and infecting monkeys by the intranasal instillation of Japanese encephalitis (JE) virus. He was vaccinated with 1 ml of attenuated yellow fever virus 17-D on July 10, 1961, 66 days before onset of symptoms of the present illness.

Physical examination on admission two days after onset of symptoms revealed bilateral facial paresis, complete lower motor neuron quadriplegia, absence of all deep tendon reflexes, and paralysis of the intercostal muscles. Vagus cranial nerve (X) involvement was manifested by nasal speech and difficulty in swallowing. There were no pathological reflexes. The abdominal and cremasteric reflexes were absent. Sensory examination revealed only loss of vibratory and position sense in the left foot. The sensorium was clear and remained so throughout the illness.

Initial laboratory data were as follows: hemoglobin, 14 gm/100 ml; hematocrit reading, 43%; white blood cell count (WBC) 9,250/cu mm; and differential count: band forms 6%; segmented forms, 66%; lymphocytes, 26%; and monocytes, 2%. A fasting eosinophile count was 50/cu mm. Corrected sedimen-

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TABLE 1.—*Hep-2 Tissue Culture Neutralization Test For Poliomyelitis Virus of Patient's Sera*

	Poliomyelitis Types, Antigen *		
	1	2	3
Serum 1 (7-10-61)	40	40	160
Serum 2 (9-15-61)	40	80	80
Serum 3 (9-16-61)	40	80	160
Serum 4 (10-31-61)	40	80	80

* Titer expressed as reciprocal of initial serum dilution.

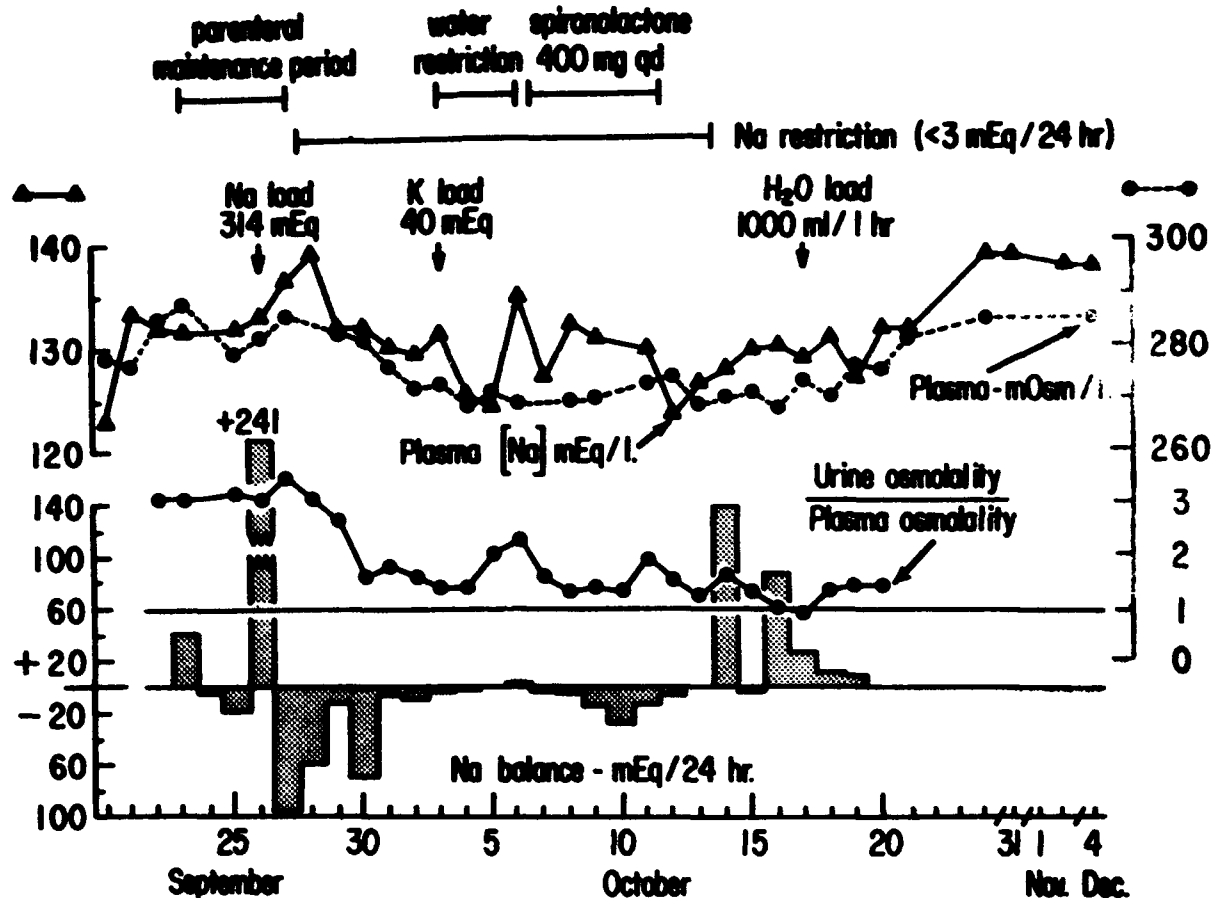
tation rate was 42 mm/hr. Lumbar puncture revealed clear cerebrospinal fluid (CSF) with normal pressures and dynamics; the fluid contained 240 WBCs/cu mm, all lymphocytes; protein, 90 mg/100 ml; and sugar, 87 mg/100 ml (simultaneous fasting blood sugar was 127 mg/100 ml). The CSF was sterile and no organisms were seen on a gram-stained smear. On Sept 20 plasma electrolytes were: sodium, 123 mEq/liter; potassium, 3.9 mEq/liter; carbon dioxide, 24.5 mEq/liter; and chloride, 97 mEq/liter. Plasma osmolality was 278 mOsm/liter; and venous blood pH was 7.40. Normal results were obtained in the following tests: urinalyses, serum protein electrophoresis, blood urea nitrogen, creatinine, bilirubin, thymol turbidity, cephalin flocculation, calcium, phosphorus, carbon dioxide content, pH, sweat sodium; heterophile agglutination titer; 17-hydroxysteroids/24-hour urine (this test was done three times: Oct 5, 18, and 23), chest x-ray, and electrocardiogram. Plasma volume measured on Sept 26, was 2,200 ml at ten minutes after intravenous injection of Evans Blue (T-1824); it was 4.2% of his body weight. Daily creatinine clearances during the first month of hospitalization ranged from 80 to 130 ml/minute. On Sept 18, a virus was isolated from material obtained by throat swab. It was shown to be JE virus by tissue culture neutralization tests and was reisolated from the original material which had been frozen. Stool and CSF cultures did not yield virus. The patient did not develop antibodies to any of the three types of polio viruses by tissue culture neutralization tests (Table 1). The patient was kept in the respirator and was given intranasal oxygen and other supportive treatment. Muscle function began to return and he was removed from the respirator on Sept 23. From Sept 23 to 27, he was given nothing by mouth but was maintained on parenteral fluids (lactated Ringer's solution; 5% and 10% dextrose in distilled water; 5% dextrose in isotonic saline; and intravenous protein hydrolysates (Amigen)—a casein hydrolysate solution). Fluid and electrolyte balance studies were done, and the following tests were performed in an attempt to characterize the patient's electrolyte disturbance: sodium loading, potassium loading, water restriction, water loading, sodium restriction, and administration of the spironolactone (Aldactone-A) near the end of the sodium-restriction period (Figure). Upon completion of the four-day study, the patient was given weighed food and measured fluids, the electrolyte composition of which could be estimated by using stand-

ard tables.⁷ The balance study was continued for an additional 23 days. All urine, stool, and vomitus collected (during the 27-day balance study period) and were measured daily. The body weight to the nearest 0.01 kg was determined daily on a bedside scale. Except for the water restriction and parenteral maintenance period, the patient was allowed water ad lib as thirst dictated; salt was given ad lib except during the sodium-restriction period. Sodium intake after the parenteral maintenance period was calculated from the difference in daily weight of the patient's sodium chloride dispenser plus the amount of sodium in his food.

On Oct 7, the second lumbar puncture revealed normal pressures and dynamics; the CSF was clear and sterile, but contained 25 WBC/cu mm, all lymphocytes, and protein 850 mg/100 ml. The spinal fluid sugar was normal. These unexpected results, together with the clinical findings, established the diagnosis of polyradiculoneuropathy of the Guillain-Barré type. The patient continued slowly to regain muscle function. On Jan 5, 1962, the third lumbar puncture revealed normal CSF pressures and dynamics and clear fluid containing 12 lymphocytes/cu mm; protein, 100 mg/100 ml; and sugar, 72 mg/100 ml. He was able to move all extremities and to sit alone for short periods when propped up. Since January graded physical therapy has been used and in March 1962, he was able to walk a few steps unsupported. In July 1964, he was able to walk with crutches, but marked muscle weakness persisted.

Comment

The paradoxical association of hyponatremia and hypotonicity of the plasma on the one hand, and hypertonicity of the urine and salt-wasting on the other hand, was first reported by Peters et al in 1950,¹ and two years later by Welt et al in patients with encephalitis, cerebral vascular disease, brain neoplasms, and bulbar polio.² Peters felt that the cause of the paradox was probably failure of corticotropin (ACTH) production with resultant decreased output by the adrenals of salt-retaining hormone; or that it was perhaps a direct nervous influence from the central nervous system to the kidney, modifying tubular sodium reabsorption. Welt showed in his cases that there was normal adrenal function, and postulated inability of the proximal tubule to conserve sodium. In 1957, Schwartz et al reported two cases associated with inoperable bronchogenic carcinoma, one with widespread cerebral metastases and the other with infiltration of the vagus nerves in the mediastinum and encephalomalacia.³ Schwartz gave documentary evidence that the electrolyte defect arose because of inappropriate secretion of



Sodium balance, plasma sodium concentration and osmolality, and ratio of urine to plasma osmolality during the initial phase of the illness.

antidiuretic hormone (ADH) from the posterior pituitary. He showed that the electrolyte disturbance could be corrected simply by withholding water. In 1959, Epstein and Levitin reported "cerebral salt-wasting" in a 19-year-old girl with convulsions and an abnormal electroencephalogram.⁴ Plasma from their patient was infused into a patient with diabetes insipidus and produced a transient decrease in free water clearance and a rise in urine osmolality, suggesting the presence of an antidiuretic factor in the girl's plasma. In 1961, Carter et al reported two patients, one with a brain tumor and another with a basilar skull fracture, in whom renal salt wastage was not prominent but water retention was prominent, thus supporting the evidence that the syndrome is caused by inappropriate ADH secretion.⁵ One of Carter's patients, while receiving 2,500 ml water daily at a constant rate, had an increase in urine osmolality despite a falling serum sodium concentration, indicating that extracellular fluid osmolality was no longer operating as a control-

ling mechanism for the secretion of ADH. The response to changes in extracellular fluid volume may continue to operate, though in a blunted manner. The explanation for the paradoxical natruresis is probably this: the expansion of extracellular volume as a result of ADH-induced water retention increases the glomerular filtration rate and suppresses the secretion of aldosterone, either of which might lead to increased sodium output in the urine. All reports of cases of this syndrome have fallen into one of two categories: (1) intrathoracic disease or (2) central nervous system disease, either functional or structural.⁶

Our patient was found to have a mild form of "cerebral hyponatremia" during the first month of his illness. The electrolyte disturbance gradually corrected itself spontaneously over a three-month period. The Figure illustrates the principal features of the electrolyte disturbance. During the first 25 days of the illness, his mean plasma sodium concentration was 130 mEq/liter and his mean plasma osmolality level was 277

mOsm/liter. The dilution of extracellular fluid would normally lead to cessation of ADH release and to a diuretic response with low urine osmolality and sodium output. However, the mean urine osmolality was 600 mOsm/liter or more than twice that of the plasma, indicating the presence of ADH. The mean urine sodium concentration for the first ten days of illness was 75 mEq/liter, evidence that the kidneys were not conserving sodium despite the low plasma sodium. The patient's clinical appearance suggested neither excess nor depletion of extracellular fluid, and the T-1824 plasma volume on Sept 25 was normal. His renal and adrenal function were normal, judged by daily creatinine clearances and urinalyses and by 17-hydroxysteroid assays and eosinophile counts. On the fourth day of the balance study, he was given 300 mEq/liter of sodium intravenously, which transiently raised the plasma sodium and osmolality to nearly normal levels. These values became subnormal again within 18 hours, however. During the four-day balance period a negative potassium balance existed, but the potassium balance became positive and remained so after oral feeding was started. Moreover, an intravenous potassium load of 40 mEq/liter was given on Oct 3, without effect on plasma sodium or osmolality values of plasma and urine.

Water restriction producing negative water balance over a 48-hour period provoked increased urine osmolality without changing plasma osmolality. Thus the patient was able to elaborate more ADH under the stimulus of extracellular volume depletion. This conforms to the view that an extracellular volume regulatory mechanism for ADH is still intact to some degree in this syndrome.⁶ Water restriction also resulted in an increase in plasma sodium concentration from 124 to 134 mEq/liter, but the plasma sodium value promptly fell again when water restriction was terminated. A water load at another time (Oct 17) resulted in lowering the urine osmolality to 165 mOsm/liter, showing that acute expansion of the extracellular volume could partially suppress the (presumed) inappropriate secretion of antidiuretic hormone.

Sodium was restricted to less than 3 mEq/liter daily for 16 days (Sept 27 to Oct 13: Figure). During this time the sodium output in the urine gradually fell, finally reaching equilibrium with the intake after eight days. Thus, aldoster-

one output probably did occur in response to increased extracellular volume resulting from negative sodium balance; the presence of aldosterone was further documented by the fact that administration of the aldosterone antagonist spironolactone near the end of the sodium-deprivation period induced an increased urinary sodium and negative sodium balance (Figure).

The Landry-Guillain-Barré syndrome, like all syndromes, is a nonspecific complex of clinical and laboratory signs and symptoms. It is inevitable that dispute will arise from time to time about what constitutes the syndrome and what does not. As more cases appeared after the original descriptions of the syndrome, it became obvious that the clinical picture could be much more pleomorphic than was present in the small series of Guillain, Barré, and Strohl.⁸ For example, these authors believed that death should not occur and that recovery should always be complete, and it is now well-known that death may occur and that recovery may be incomplete.^{9,10} Probably the most apt definition of the syndrome is the one given by Haymaker and Kernohan in their review⁹:

A polyradiculoneuropathy which may begin in any peripheral neurons, spinal or cranial, circumscribed or wide-spread, may affect predominantly the motor or the sensory neurons or both to the same degree; it may extend into the central nervous system at any point, and either ascend or descend, the outcome usually being dependent on the degree of involvement of respiratory or cardiac nerves. Changes in the amount of protein and the number of cells in the spinal fluid are regarded as incidental to the disorder.

The Guillain-Barré syndrome has been reported in Cushing's disease, multiple myeloma, infectious mononucleosis, brucellosis, diphtheria, infectious hepatitis, epidemic encephalitis, peritonsillar abscess, and in other types of infectious disease.¹¹ In about 50% of cases the syndrome follows as a "second illness" one or two weeks after an upper-respiratory-tract infection, suggesting delayed hypersensitivity. In recent years, the idea that the syndrome may be an allergic process has received considerable attention: (1) In autopsied cases an outstanding feature is marked edema of the nerve fibers of the spinal roots and proximal portions of the cranial and peripheral nerves. Cellular infiltration is minimal. Hyperemia of the meninges is often found.^{9,12} (2) The syndrome has been known to follow the administration of anti-

TABLE 2.—*Hemagglutination Inhibition Tests—Group-B Arboviruses*

HI Titers of Sera Determined Simultaneously and Exactly the Same Laboratory Conditions								
Patient	Serum Collected	Remarks	Japanese Encephalitis *	St. Louis Encephalitis	West Nile Encephalitis	Russ. Spr-Sum. Encephalitis	Dengue 1	Dengue 2
1	7-10-61	Yellow fever vaccination	10 (CF+ 32)	320	320	80	320	80
	8-15-61		10 (CF >128)	5,120	2,560	640	640	640
	9-16-61	Disease onset 9-14-61	640 (CF >128)		640	1,280	2,560	
	10- 3-61		1,280 (CF >128)	5,120	20,480	5,120	5,120	
Other Technicians								
2	7-10-61	Yellow fever vaccination	320	640	640	320	320	320
	8-15-61		640	2,560	2,560	640	1,280	340
	9-16-61		640		640	640		
3	7-10-61	Yellow fever vaccination	40	80	160	40	40	
	8-15-61		40	160	160	80	80	80
	10- 4-61					40		
4	7-10-61	Yellow fever vaccination	40	640	640	320	320	160
	8-15-61		320	320	640	640	320	320
	10- 4-61					160		
5	7-10-61	Yellow fever vaccination	10	10	20	10	10	10
	8-15-61		20	20	20	10	10	10
	10- 4-61					10		

* Complement fixation titer.

† In most instances each test was repeated one or two times. The technique used for the HI test has been reported elsewhere.¹⁰

rabies inoculation, typhoid vaccine, tetanus antitoxin, pertussis and antipneumococcic vaccines, human serum, and smallpox vaccination. In one case reported by Kisch¹³ the syndrome followed smallpox vaccination in a woman vaccinated twice before who had a severe "primary take." (3) A disease called experimental allergic neuritis has been produced in rabbits by injecting them with rabbit sciatic nerve or spinal ganglia. This disease has many of the clinical features of the Guillain-Barré syndrome in man, and in addition, there is high protein and low cell count in the spinal fluid of the affected rabbits.¹⁴ (4) Finally, complement-fixing antibodies to human nervous tissue antigens have been demonstrated recently in patients with the Guillain-Barré syndrome.¹⁵

There have been few immunologic data to support the theory of a hyperimmune or hypersensitivity response to some agent in the Guillain-Barré syndrome. In 1953, Boshes and Sherman reported a case in which the patient had had the "flu" three months before and again two weeks before the appearance of his paralysis.¹⁰ Viral complement-fixation tests suggested an anamnestic response to influenza antigen. Casals has shown that within the B group of arboviruses there are immunologic synergistic group responses following natural or artificial infection, especially pronounced in the hemagglutination-inhibition (HI) test but also ap-

parent in the complement-fixation and neutralization tests.¹⁰ The cross-response is more pronounced after a second infection with any of the group-B viruses than after the first infection.

The HI antibody titers in our case show a marked immunologic response to the group-B arboviruses. On July 10, 1961, our patient received a vaccination with 1 ml of living yellow fever virus type 17-D, which, like JE, is one of the group-B arboviruses. At the time of vaccination, the patient's HI titers were moderately low (Table 2). On Aug 15, one month prior to onset of paralysis, the titers had risen two to sixteen-fold. By Sept 16, two days after admission, the titers had again increased, and two weeks after onset of illness (Oct 2) the HI titers were 32 to 128 times the July 10 values; the HI titer to JE virus was 100 times the July 10 titer. The patient had been working closely with group-B arboviruses until onset of his disease in mid-September, with the possibility of repeated exposure to them. Indeed, JE virus was cultured from his throat at the onset of the paralytic illness.

Table 2 shows the HI antibody response of four technicians who were working in the same virus laboratory and in as close contact with the group-B arboviruses as the patient. These technicians received 1 ml of yellow fever vaccine on the same date as the patient. Their titer in-

creases of zero to eightfold are of the magnitude expected after such a vaccination.

The possibility was entertained that our patient's illness was actual clinical Japanese encephalitis, but the following arguments led us to reject this idea: (1) His clinical picture was decidedly one of a polyradiculoneuropathy and there was no evidence of encephalitis. (2) In vivo mouse neutralization antibody tests performed on serum of July 25, 1960, gave a neutralization index of 3.7. This highly significant figure is evidence that the patient had profound natural immunity to JE virus one year prior to onset of his illness. (3) Complement-fixation tests performed on the patient's serum show that a fourfold rise in titer to JE virus had already occurred one month prior to onset of clinical illness (Table 2). (4) Cerebrospinal fluid, taken at the same time the throat culture was obtained, failed to yield JE virus. (It should be pointed out that attempts to isolate JE virus from the spinal fluid of patients with obvious clinical Japanese encephalitis have rarely, if ever, been successful.) If only laboratory criteria were used, we would have to diagnose in the patient all the group-B arbovirus infections (Table 2). He may have had infection with JE virus, but we feel he did not have overt disease caused by JE virus. Infection is not synonymous with disease.

It is impossible to reach a firm decision regarding the actual cause of the patient's neuropathy: infection with JE virus or hypersensitivity to the virus. We interpret the following sequence of events as presumptive evidence for development of neuroallergy which was manifested as a polyradiculoneuropathy of the Guillain-Barré type: Our patient had repeated antigenic experience with the group-B arboviruses; he acquired at least one of them (JE virus) as part of his pharyngeal flora; he developed extremely marked antibody responses to these viruses. The yellow fever vaccination two months prior to onset of clinical disease may well have provoked an anamnestic antibody response to JE virus as well as to all the other group-B arboviruses,¹⁶ since he probably had inapparent JE infection in childhood (there is immunologic evidence that 97% of adult Taiwanese have had JE-virus infection in childhood).¹⁷

Two tests which might be applied in any given case of Guillain-Barré syndrome with a suspected allergic etiology are the Prausnitz-Kustner skin test and an assay of serum complement such as Lange et al used to distinguish glomerulonephritis from other renal diseases.¹⁸ The former might detect skin sensitivity reagins in the serum of the patient and the latter might indicate a widespread antigen-antibody reaction with utilization of serum complement. These two tests used in conjunction with determinations of antibody response by standard serological tests would permit the presumption of an allergic etiology in any particular case. More critical techniques must be applied, however, before allergy can actually be proven to be a cause of the Guillain-Barré syndrome.

Summary

While working in the laboratory with group-B arboviruses, a Taiwanese laboratory technician developed an illness indistinguishable from the Guillain-Barré syndrome and at the same time was observed to have the so-called cerebral salt-wasting syndrome. The electrolyte disorder was studied in some detail. It was self-limited, improving in conjunction with deferescence of the patient's acute phase of illness, and lasted about 30 days. This disturbance has not previously been reported to occur with the Guillain-Barré syndrome.

The patient had extremely marked hemagglutination-inhibition antibody responses to the group-B arboviruses, and especially to Japanese encephalitis virus, which increased one hundredfold in titer. It is proposed that hypersensitivity to the group-B arboviruses may have played a role in the patient's illness.

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Generic and Trade Names of Drugs

Protein hydrolysates (intravenous)—Amigen, Aminosol, Hyprotigen, Parenamine, Travamin.
 Spironolactone—Aldactone-A.
 Corticotropin—ACTH, Acthar, Corticotropin.

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